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## Asthma, allergy and the Olympics

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**Abstract:** **OBJECTIVE:** There are no comprehensive surveys relating the reported high prevalence of asthma and allergic diseases in athletes to comorbidities and immune changes associated with intense chronic exercise. This 12-year survey aims to evaluate several clinical, functional and immunological parameters in order to assess features, trend and burden of asthma, allergy, infections and autoimmune diseases, in a large homogeneous population of Olympic athletes. **METHODS:** Six hundred and fifty-nine Italian Olympic athletes were studied through four cross-sectional surveys performed between 2000 and 2012 before the Summer and Winter Olympics. Clinical diagnosis of allergic, autoimmune and infectious diseases was complemented by: skin-prick tests ( $n = 569$ ); pulmonary function tests ( $n = 415$ ); total ( $n = 158$ ) and specific ( $n = 72$ ) serum IgE; serum autoantibodies ( $n = 30$ ), cytokines and growth factors ( $n = 92$ ); flow cytometry ( $n = 135$ ). **RESULTS:** The prevalence of asthma and/or exercise-induced bronchoconstriction was 14.7%, with a significant increase ( $P = 0.04$ ) from 2000 (11.3%) to 2008 (17.2%). The prevalence of rhinitis, conjunctivitis, skin allergic diseases and anaphylaxis was 26.2%, 20.0%, 14.8% and 1.1%, respectively. Sensitization to inhalant allergens was documented in 49.0% of athletes, being 32.7% in 2000 and 56.5% in 2008 ( $P < 0.0001$ ). Food, drug and venom allergy was present in 7.1%, 5.0% and 2.1% of athletes, respectively. The high prevalence of asthma and allergy was associated with recurrent upper respiratory tract (10.3%) and herpes (18.2%) infections, an abnormal T cell subset profile and a general down-regulation of serum cytokines with a significantly lower IFN- $\gamma$ /IL-4 ratio. **CONCLUSION:** A chronic and intense physical exercise may cause a transient immunodepression with a preferential shift to a Th2 response, associated with abnormalities of the respiratory tract.

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# Asthma, allergy and the Olympics: a 12-year survey in elite athletes

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## Objective

There are no comprehensive surveys relating the reported high prevalence of asthma and allergic diseases in athletes to comorbidities and immune changes associated with intense chronic exercise. This 12-year survey aims to evaluate several clinical, functional and immunological parameters in order to assess features, trend and burden of asthma, allergy, infections and autoimmune diseases, in a large homogeneous population of Olympic athletes.

## Methods

Six hundred and fifty-nine Italian Olympic athletes were studied through four cross-sectional surveys performed between 2000 and 2012 before the Summer and Winter Olympics. Clinical diagnosis of allergic, autoimmune and infectious diseases was complemented by: skin-prick tests ( $n=569$ ); pulmonary function tests ( $n=415$ ); total ( $n=158$ ) and specific ( $n=72$ ) serum IgE; serum autoantibodies ( $n=30$ ), cytokines and growth factors ( $n=92$ ); flow cytometry ( $n=135$ ).

## Results

The prevalence of asthma and/or exercise-induced bronchoconstriction was 14.7%, with a significant increase ( $P=0.04$ ) from 2000 (11.3%) to 2008 (17.2%). The prevalence of rhinitis, conjunctivitis, skin allergic diseases and anaphylaxis was 26.2%, 20.0%, 14.8% and 1.1%, respectively. Sensitization to inhalant allergens was documented in 49.0% of athletes, being 32.7% in 2000 and 56.5% in 2008 ( $P<0.0001$ ). Food, drug and venom allergy was present in 7.1%, 5.0% and 2.1% of athletes, respectively. The high prevalence of asthma and allergy was associated with recurrent upper respiratory tract (10.3%) and herpes (18.2%) infections, an abnormal T cell subset profile and a general down-regulation of serum cytokines with a significantly lower IFN- $\gamma$ /IL-4 ratio.

## Conclusion

A chronic and intense physical exercise may cause a transient immunodepression with a preferential shift to a Th2 response, associated with abnormalities of the respiratory tract.

## Keywords

allergy, asthma, infection, athlete, exercise

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## INTRODUCTION

Several studies [1–3] called attention to a high prevalence of asthma in athletes, ranging from 22.8 to 54.8% depending on the type of sport discipline and on criteria used for diagnosis. However, independently from the above potential confounders, studies performed in Olympic teams before 2000 show that the prevalence of asthma in elite athletes is high and increasing, from 9.7% in 1976 to 21.9% in 1996 in the Australian Olympic delegation [4,5], and from 11.2% in 1984 to 16.7% in 1996 in the US Olympic delegation [6,7]. Asthma in elite athletes appears to be a distinct phenotype [8–12] which needs adequate attention and management considering that 23.1% of the 263 sudden deaths in athletes reported by Becker *et al.* [13] occurred in asthmatic athletes.

In addition to the high prevalence of asthma and airway hyperresponsiveness, an increased reported risk of upper respiratory tract infections (URTIs) has been reported in elite athletes [14,15]. Both viruses (rhinovirus, influenza and parainfluenza viruses, adenovirus and coronavirus) and bacteria (streptococci and staphylococci) are claimed to be involved in causing URTI in athletes, although data from large systematic studies including the isolation and identification of the responsible agents are still very limited.

Although URTIs have been shown to be followed by wheezing in athletes [16], allergy is considered to be the major risk factor for asthma in this population. In fact, the risk of asthma increases 25-fold in atopic speed and power athletes, 42-fold in atopic long-distance runners and 97-fold in atopic swimmers [17].

As for asthma, sensitization to common allergens and allergic diseases has been reported to have a high and increasing prevalence in elite athletes [18–20]. Allergic rhinitis has been documented in 16.8 [18] to 29.5% [5] of athletes, affecting their performances and quality of life [21]. Moreover, prospective studies in the general population indicate that rhinitis frequently precedes the onset of asthma representing a risk factor for it [22]. Allergic skin diseases are also often observed, favored by several factors related to exercise, as well as by contact with sport materials and instruments (warming or cooling, sweating, sun exposure, pressure, rubber vests, etc.) [23]. At last, exercise-induced anaphylaxis, a life-threatening condition, has been reported in this peculiar population often in relation to ingestion of food a few hours before exercising [24].

In contrast to the numerous reports on asthma and allergy in athletes, data on the prevalence of autoimmune diseases and circulating autoantibodies in this peculiar population are scarce,

although some clinical pictures reported with a higher prevalence in athletes, such as amyotrophic lateral sclerosis (Gehrig disease), have been referred to autoimmune phenomena [25].

The mechanisms underlying the epidemiological evidence of a close relationship between intense exercise and asthma and/or immune diseases are not fully elucidated. In fact, although an acute exercise challenge has been shown to represent a stress event inducing several immunological changes, few data are available on the effects of intense and chronic exercising on the immune system [26].

Olympic athletes represent a unique model of regular intense physical training undergoing increasing loads of work in the period preceding the Games.

This 12-year study aims to evaluate several clinical, functional and immunological parameters in order to assess features, trend and burden of asthma, allergy, infections and autoimmune diseases, in a large homogeneous population of Olympic athletes studied with the same methodologies in four cross-sectional surveys performed on the occasions of the Sydney (2000), Beijing (2008), Vancouver (2010) and London (2012) Olympics. This comprehensive approach also might help to generate hypothesis on the possible effects of an intense and chronic physical exercise in health or disease.

## METHODS

### Study design

In 659 athletes selected to be a part of the Italian Olympic Delegation at Summer (Sydney 2000, Beijing 2008 and London 2012) and Winter (Vancouver 2010) Olympics, clinical data were collected through history taking, standardized validated questionnaires [27] and medical examination, with special reference to the presence of sensitization and allergic diseases, asthma, URTI and autoimmune diseases.

The following clinical, functional and immunological parameters were also collected, depending on athlete and sample availability with no pre-planned clinical selection criteria, in order to answer specific epidemiological and mechanistic study questions:

- (1) Skin test reactivity to common allergens (n = 569)
- (2) Pulmonary function tests (n = 415)
- (3) Total serum IgE determination (n = 158)
- (4) Specific serum IgE determination (n = 72)
- (5) Serum autoantibodies (n = 30)

- (6) Flow cytometry (n = 135)  
 (7) Serum cytokine and growth factor levels (n = 92)

The same diagnostic criteria and procedures were adopted on the occasion of all surveys.

### Study population

Six hundred and fifty-nine athletes (sex 441 men, 218 women, age range 16–40, mean  $27.0 \pm 5.5$  years) were studied. The 30 sport disciplines practiced were grouped according to standard classifications based on environmental exposure, metabolic pathways and cardiovascular risk (Table 1).

Data were collected in distinct cross-sectional studies, performed within 6 months before the Olympic Games, during an intense training period. The Sydney and Beijing surveys performed in a wide population of athletes were mainly aimed at evaluating the changing prevalence of asthma and allergy 8 years apart. Smaller population samples were studied in Vancouver to evaluate differences, if any, between summer and winter sports and in London to assess intraindividual variability of pulmonary function and compliance to the treatment of the asthmatic athletes already included in the Beijing survey.

Informed written consent was obtained by all athletes. Data were treated in respect of privacy and ethical requirements. The study was approved by the Internal Review Board of the Italian National Olympic Committee.

### Study procedures

Study procedures are reported in detail in the online repository material (Supplemental Digital Content 1, <http://links.lww.com/COAI/A12>).

### Diagnostic criteria

Diagnosis of asthma and degree of disease control were made according to Global Initiative for Asthma (GINA) guidelines ([www.ginasthma.org](http://www.ginasthma.org)) on the basis of a comprehensive evaluation of history, questionnaires, medical examination, pulmonary function tests and bronchial challenges. Athletes with exercise-induced bronchoconstriction (EIB) were considered as asthmatic patients even in the absence of clinical asthma.

Rhinitis, conjunctivitis, allergic skin diseases, anaphylaxis and autoimmune diseases were diagnosed according to standard clinical criteria and international and national guidelines for these diseases, with special reference to criteria set for athletes [3,19,28]. Athletes were defined as allergic in the presence of at least one positive sensitization to allergens at skin tests.

**Table 1.** Sport disciplines and categories

Sport disciplines	Number of athletes
Archery	3
Athletics	55
Baseball	54
Basketball	22
Boxing	12
Canoe/Kayak	53
Cycling	46
Equestrian	19
Fencing	28
Field hockey	11
Figure skating	7
Football	25
Golf	5
Gymnastics	22
Judo	32
Modern pentathlon	3
Rowing	52
Sailing	16
Shooting	37
Skiing	15
Swimming	16
Table tennis	5
Taekwondo	7
Tennis	31
Triathlon	1
Volleyball (beach)	17
Volleyball (indoor)	31
Water polo	21
Weightlifting	5
Wrestling	8
Total	659
Sport categories	
Outdoor/indoor	443/216
Aerobic/anaerobic/mixed	234/209/216
Low/high cardiovascular risk	50/609

URTI and herpes infections were diagnosed on the basis of clinical criteria without identification and isolation of the responsible agents.

### Statistical analysis

Statistical analysis was done using parametric or nonparametric tests, depending on the data distribution of the variables under study, through the SPSS19 software (IBM, Armonk, New York, USA). *P* values <0.05 were considered as significant.

## RESULTS

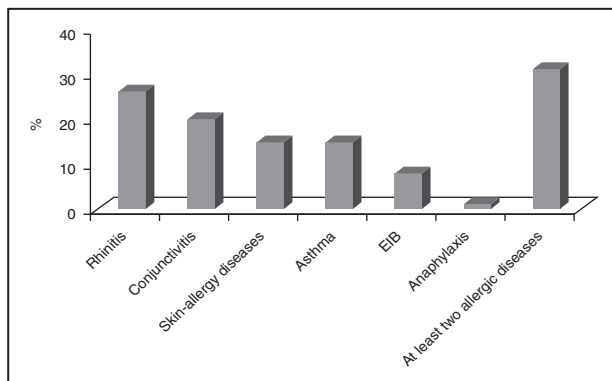
### Asthma and allergy in Olympic athletes

The prevalence of asthma in the 659 athletes studied was 14.7% (Fig. 1). In the 97 athletes defined as asthmatic patients, a previous doctor diagnosis of asthma was made in 61.9% of cases, whereas 81.7% referred respiratory symptoms suggestive of clinical asthma. Asthma appeared not to be under control in 18.6% of athletes; however, only half of them were using antiasthmatic drugs at the time of observation. EIB was present in 8.1% of athletes, being associated with clinical asthma in 64.8% of cases.

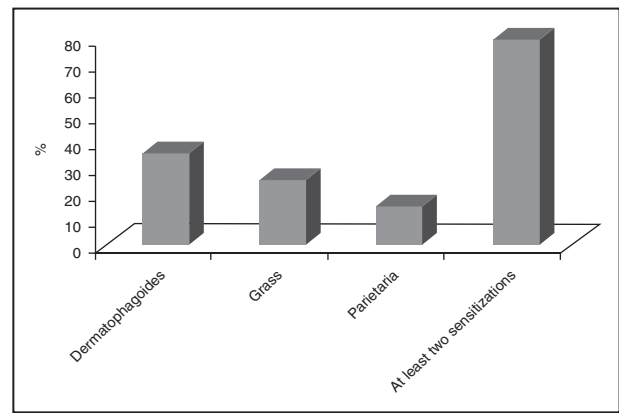
Mean values of forced expiratory volume in the 1st second (FEV<sub>1</sub>) ( $107.7 \pm 13.3\%$  of predicted) and forced expiratory flow (FEF)<sub>25–75</sub> ( $95.2 \pm 21.4\%$  of predicted) in asthmatic athletes were not significantly different from those of healthy athletes ( $108.6 \pm 12.8\%$  and  $96.3 \pm 21.9\%$ , respectively). Furthermore, 68.2% of asthmatic athletes had FEV<sub>1</sub> values more than 100% of predicted, whereas only 7.2 and 14.0% had abnormal FEV<sub>1</sub> (less than 80% of predicted) and FEF<sub>25–75</sub> (less than 70% of predicted) values, respectively.

A positive bronchodilator test was observed only in athletes with clinical asthma and abnormal FEV<sub>1</sub> basal values at the time of testing. At least one positive bronchoprovocative challenge for documenting EIB was found in 75.0% of the athletes tested (those with a suspected diagnosis and FEV<sub>1</sub> greater than 80%), independently from the presence of clinical asthma. Pulmonary function data collected in athletes who took part in both the Beijing and London Olympics, in spite of nonclinically relevant intraindividual variability overtime, did not show any significant difference between the two surveys.

The prevalence of rhinitis, conjunctivitis, skin allergic diseases and anaphylaxis was 26.2, 20.0,



**FIGURE 1.** Prevalence of asthma, EIB and allergic diseases in the 659 Olympic athletes. EIB, exercise-induced bronchoconstriction.



**FIGURE 2.** Relative prevalence of sensitization to main inhalant allergens at skin tests in the 569 Olympic athletes.

14.8 and 1.1%, respectively. In 31.1% of athletes, two or more allergic diseases were present (Fig. 1).

Sensitization to at least one inhalant allergen was documented by skin tests in 49.0% of the 569 athletes tested. *Dermatophagoides* (35.0%), grass (25.0%) and *Parietaria* (14.7%) represented the allergens more frequently responsible for sensitization (Fig. 2); 79.0% of skin-positive athletes had more than one sensitization.

The type of sport disciplines and categories did not significantly influence the prevalence and pattern of sensitization or allergic disease. However, a reliable multivariate analysis was not possible due to the low number of athletes in homogeneous subgroups defined by taking into account the sport categories in each sport discipline.

Food, drug and venom allergy was present in 7.1, 5.0 and 2.1% of athletes, respectively. Three out of the seven cases of anaphylaxis were associated with food allergy.

When data on disease and allergy were matched, a clinically relevant sensitization was present in over two-thirds of the symptomatic athletes. In particular, asthma was shown to have an allergic origin in 85.1% of cases.

The comparison of asthma and allergy prevalence rates between the Sydney and Beijing Olympics (Table 2) showed a consistent increase for all clinical phenotypes, which was significant for asthma ( $P = 0.049$ ), allergic skin diseases ( $P = 0.018$ ) and sensitization ( $P = 0.0001$ ). On the contrary, there were no differences in the relative prevalence of allergens causing sensitization, although the number of polysensitized athletes increased from 62.5% in 2000 to 85.0% in 2008.

Only 23.8% of allergic symptomatic athletes had ever received antiallergic/antiasthmatic treatment. On the contrary, a high proportion of athletes (34.1%) had received supplements and drugs



**Table 2.** Prevalence of asthma, allergic diseases and sensitization to inhalant allergens in two cross-sectional surveys

Survey	Asthma	Rhinitis	Conjunctivitis	Skin diseases	More than one allergic diseases	Sensitization
Sydney 2000	30/266 (11.3%)	67/266 (25.3%)	50/266 (18.8%)	29/266 (10.9%)	83/266 (31.2%)	81/248 (32.7%)
Beijing 2008	65/378 (17.2%)	102/378 (27.0%)	79/378 (20.9%)	68/378 (18.0%)	150/437 (34.3%)	174/308 (56.5%)
Statistical significance	$P = 0.0494$	$P = 0.695$	$P = 0.578$	$P = 0.018$	$P = 0.445$	$P < 0.0001$

(mainly nonsteroid anti-inflammatory drugs) in the week before examination. Six of the seven asthmatic athletes, who participated in both the Beijing and London Olympics, showed a very poor compliance to the treatment prescribed according to GINA guidelines and in respect of the World Anti-Doping Agency (WADA) regulation. Data on smoking habits available in 378 athletes showed a prevalence of smokers in 18%.

The prevalence of asthma and allergy was not significantly different between pre-Olympic athletes who qualified for the Games and those who could not qualify. Six medals out of the 23 obtained by the Italian athletes studied were won by allergic/asthmatic athletes.

**Infections and autoimmunity in Olympic athletes**

The prevalence of recurrent infections was particularly high in athletes, although the lack of data from a matched general population prevents understanding the magnitude and relevance of this finding; 10.3% of athletes had more than three URTI and 18.2% of athletes had more than one relapse of herpes infection in the last 12 months. The prevalence of URTI was not significantly different between Sydney 2000 and Beijing 2008.

No clinical autoimmune disease was present in any of the athletes studied. The presence of autoantibodies of potential clinical relevance, tested in a pilot study (n = 30 athletes), was only found in two apparently healthy young female athletes (very high titers of thyroid peroxidase antibodies in one case and a homogeneous immunofluorescence pattern of anti-nuclear antibodies, associated with border-line titers of anti-centromere antibodies in the other case).

**Immunological profile in Olympic athletes**

Total serum IgEs were significantly higher in allergic than in nonallergic athletes (median values 105 kU/l; CI 95% 83.0–160.0 kU/l vs 38 kU/l; 27.4–50.5 kU/l;  $P = <0.05$ ). However, both allergic and nonallergic athletes had total serum IgE values within the range reported in a sedentary matched sample of the Italian general population.

In 16.0% of polysensitized asthmatic athletes, specific IgE to molecular allergen components were directed against cross-reacting allergens (profilins, PR-10). Allergens at risk for severe allergic reactions (Ara h 1,2,3; Pru p 3; Cor a 8; omega-5 gliadin) were furthermore detected in 6.0% of all polysensitized athletes tested, even in the absence of clinical symptoms.

Mean values of circulating leukocyte subsets identifiable by flow cytometry with the panel of monoclonal antibodies used were within the

normal levels. However, abnormal values were recorded in individual cases: 43.7% of the 135 athletes studied had increased circulating basophils and 11.1% increased circulating eosinophils. A reduced absolute number of CD3<sup>+</sup> cells and natural killer cells were found in individuals, often associated with URTI and recurrences of herpes labialis infections. The ratio between CD4<sup>+</sup> cells and CD8<sup>+</sup> cells was increased in 20.7% of athletes. However, no clear-cut correlation was found between any single-cell subset abnormality and the clinical status (allergy and/or susceptibility to infections).

Serum levels of all cytokines and growth factors measured (Table 3) – except IL-13, macrophage inflammatory protein-1 alpha (MIP-1alpha) and TNF $\alpha$  – were significantly lower in athletes than in the 49 healthy sedentary matched controls ( $P < 0.05$ ). This downregulation was particularly significant for IL-1ra, IL-8, IL-12, PCP-1, IFN- $\gamma$ , platelet-derived growth factor and vascular endothelial growth factor ( $P < 0.0001$ ). No difference was observed between allergic and nonallergic athletes, except for G-CFS which was significantly lower in allergic athletes ( $P < 0.01$ ). The median value of the IFN- $\gamma$ /IL-4 ratio was significantly lower ( $P = 0.03$ ) in allergic athletes (27.8) than in both nonallergic athletes and controls (37.7 and 39.0, respectively).

## DISCUSSION

This 12-year study provides data on the prevalence of allergic diseases in relation to comorbidities and immune changes, in one of the largest population of Olympic athletes ever studied.

The prevalence of asthma appears to be high (14.7%) and significantly increased from 11.3% in 2000 to 17.2% in 2008 in Summer Italian Olympic athletes. This finding has been previously reported in studies performed before 2000 in other national Olympic delegations [3,5–8]. However, the use of the same study protocol and methodology in different cross-sectional surveys allows us to more accurately evaluate the increasing trend of this morbid condition, as well as to provide updated information in a large population of athletes. Our study did not include a control group. However, large epidemiological studies performed in Italy in a matched sedentary population sample reported a prevalence of asthma ranging from 3.3 to 7.1% and only increasing from 4.6% in 1997–2000 to 6.6% in 2007–2010 [29].

Epidemiological data and evidence emerging from the clinical, functional and immunological variables studied may also suggest mechanisms which contribute to the complex relationships between physical activity and health or disease.

A possible reason for the high prevalence of asthma found in our study might be related to the criteria used for the diagnosis and the complex relationships between asthma and EIB. The diagnosis of asthma in this study, following the criteria requested by the IOC to permit the use of  $\beta_2$ -agonists in Beijing, included among asthmatic athletes also athletes with no clinical history of asthma but with airway hyperresponsiveness after various bronchial challenges. In fact, EIB may occur both in athletes with asthma not under control and in athletes without clinical asthma [10]. EIB in athletes without clinical asthma accounted for about 20% of athletes diagnosed as asthmatic patients. However, even after excluding the cases with EIB only (19/97), the prevalence of asthma remains still high (11.8%).

Asthma and/or EIB are reported more frequently in some sports (such as endurance disciplines, swimming and winter sports) that expose athletes to an increased ventilation in particular environmental conditions (presence of allergens and pollutants, chlorine, cold air, etc.) [3]. This finding, however, could not be confirmed in our study. The prevalence of asthma in swimmers or in athletes participating in the Winter Vancouver Olympics was, in fact, not significantly different from that of summer athletes. However, the limited number of athletes in each sport discipline does not allow disproving of data previously reported in larger population samples.

A possible second reason for the high prevalence of asthma in our Olympic delegation is the higher prevalence of allergy, a well known risk factor for asthma development [17]. The prevalence of a sensitization to at least one allergen at skin tests was found in almost 50% of athletes. This very high sensitization rate was also associated with a higher prevalence of other allergic diseases, such as allergic rhinitis, conjunctivitis and skin diseases (one athlete out of three suffering from one or more allergic diseases).

Interestingly, suffering from asthma and allergy did not affect the quality of performances and the chance of qualifying for the Olympics or winning a medal. In fact, there was no statistically significant difference in the prevalence of asthma and allergy between athletes who qualified for the Olympics and those who did not qualify; furthermore, out of the 26 medals won in Beijing by 24 of the Italian Olympic athletes studied, eight were won by allergic athletes (two with asthma). This confirms that asthmatic athletes and allergic athletes may compete at the highest level if adequately diagnosed and treated [30].

As for asthma, the prevalence of allergy significantly increased from 2000 to 2008, with a very high rate of polysensitized athletes in more recent years.

**Table 3.** Median serum values (and range) of cytokines and growth factors in 41 Olympic allergic athletes, 51 NAA and 49 sedentary controls

	Median (range) pg/ml		P value (Mann-Whitney U test)	
	Allergic athletes	NAA	Allergic athletes vs controls	NAA vs controls
IL-1ra	100.9 [0–1653.8]	75.6 [0–431.4]	267.89 [56.2–847.2]	<0.0001
IL-4	2.4 [0.7–6.9]	1.7 [0–8.5]	3.17 [1.2–10]	<0.0001
IL-6	0 [0–21.6]	0 [0–140.2]	6.54 [0–97.9]	<0.05
IL-7	2.2 [0–13.3]	1.6 [0–37.5]	6.18 [0.1–27.2]	<0.0001
IL-8	8.6 [0–24.5]	8.6 [0–85.6]	38.63 [16–313.5]	<0.0001
IL-10	0.6 [0–23.8]	0.8 [0–7.5]	2.34 [0–19.1]	<0.05
IL-12	0 [0–68.2]	0 [0–56.6]	27.635 [0–225.8]	<0.0001
IL-13	2.1 [0–63.2]	1.4 [0–58.6]	3.57 [0–97.9]	NS
IL-17	0 [0–117.4]	0 [0–99.6]	9.02 [0–307.3]	<0.05
IFN- $\gamma$	71.8 [0–442.3]	63.2 [0–1432.8]	132.67 [22.4–1565.4]	<0.0001
TNF- $\alpha$	0 [0–533.2]	0 [0–69.2]	0 [0–691.2]	NS
RANTES	3586.4 [2354.4–5284.2]	3599.2 [2521.5–9412.5]	7411.105 [3120.9–19918.9]	<0.0001
IP-10	829 [403.4–1684.1]	893.5 [216.5–5748.1]	1159.9 [679–4597.5]	<0.05
MCP-1	5.4 [0–143.5]	5.4 [0–130]	117.17 [36.7–445.6]	<0.0001
MIP-1a	0.6 [0–18.9]	0 [0–20.8]	1.24 [0–50.1]	NS
MIP-1b	69.5 [23.8–168.5]	64.9 [10–195.9]	164.64 [61.5–359.4]	<0.0001
Eotaxin	40.5 [0–283.2]	39.1 [0–463]	203.38 [31–601.4]	<0.0001
G-CSF	5.5 [0–19.8]	8.2 [0–83.5]	13.74 [0–137.8]	<0.05
PDGF	4243.4 [986.1–11618.9]	3604.7 [492.9–17556.1]	11712.38 [5649–29297.7]	<0.0001
VEGF	9.7 [0–1426.5]	8.7 [0–91.2]	128.255 [11.2–530.3]	<0.0001

NAA, nonallergic athletes.



Because the relative prevalence of specific sensitizations was similar to that of the general population and no difference was observed in relation to environmental exposure (indoor vs outdoor disciplines), the high sensitization rate in athletes does not appear to be related to specific sport allergens but rather to an effect of chronic and intense exercise on a polyclonal IgE response.

The above clinical findings and the immunological data presented may allow a comprehensive interpretation of the effect of chronic and intense physical activity in elite athletes.

Our Olympic athletes showed a high prevalence of sensitization associated with increased serum total and specific IgE and circulating basophils and eosinophils, as well as a high prevalence of mucosal infections, often associated with an abnormal T-cell profile and a general downregulation of most of the cytokines tested with a low IFN- $\gamma$ /IL-4 ratio. On the contrary, no evidence of clinical autoimmune diseases or increased circulating auto-antibodies was found. These findings might confirm the hypothesis that chronic and intense physical exercise may affect the Treg/Th1/Th2 balance with a preferential shift to a Th2 immune response [31–33]. However, the higher prevalence of asthma and rhinitis in athletes may certainly recognize additional factors, which affect target organs independently from their effects on the immune function such as those reported for asthma and related to hyperventilation with a bypass of the nasal filter.

Therefore, although a moderate physical activity has been shown to represent a beneficial lifestyle factor for maintaining health and preventing obesity and chronic inflammatory diseases [34], excessive training may represent a stress event with potential negative influences on the immune response that should be adequately monitored and prevented.

Our findings may also reflect some practical implications for the management of elite athletes and, in general, of all exercisers at competitive and noncompetitive levels.

Firstly, medical examination of competitive exercisers and elite athletes is at present confined – as far as it concerns allergic diseases – to physical examination and baseline pulmonary function tests, which in this study and in our experience [35] was shown to have a very limited predictive value. Data presented indicate that asthma is often underdiagnosed (only 61.9% of athletes had a previous doctor's diagnosis of asthma) and very often undertreated (only half of the 18.6% of athletes with asthma not under control were receiving treatment). Furthermore, although allergy was shown to be a major risk factor for asthma [17]

and present in 85.1% of our asthmatic athletes, allergy diagnostics is not a part of the routine medical examination. Specific questionnaires for athletes, such as the Allergy Questionnaire for Athletes (AQUA) [27] used in our study, may help in identifying athletes with clinical or subclinical allergy and bronchial hyperresponsiveness after exercise in spite of normal spirometric values, to be eventually submitted to further appropriate investigations.

With reference to the relevance of allergy testing in athletes, it should also be noted that food allergy was present in 7.1% of our athletes, not infrequently associated with anaphylaxis. Therefore, component-resolved diagnosis of specific or cross-reacting allergens may be very helpful in polysensitized athletes for diagnosing food allergy and preventing severe asthma and anaphylaxis [36].

It must be also noted that the occurrence of asthma exacerbations, URTI and allergy symptoms at the time of competition, apart from affecting athletes' health, may significantly impair their performances. Monitoring of asthma control should therefore be mandatory, as well as standardized immunological markers should be defined to plan training programs and avoid the transient immune imbalance associated with overtraining. Preventive measures should also include a vigorous campaign for cessation of smoking, which was a frequent habit in our study, unexpected for an elite sport population and regrettably observed even in asthmatic athletes.

At last, our study indicates that although over-medication is a common practice in athletes, only a small proportion of those with asthma and/or allergy (almost one athlete out of four) have ever received an antiasthmatic/antiallergic treatment, very often not in agreement with the International Guidelines. Furthermore compliance to treatment in our study was shown to be very poor. First-generation antihistamines, often used, not only affect vigilance and physical performances but may represent a danger for their potential cardiovascular side-effects. It is also unexpected that long-acting beta-2 agonists (LABAs), in contrast to Food and Drug Administration-European Medicines Agency warnings [37] and in view of the reported onset of tolerance [38,39], were often used in our athletes to prevent EIB without the concomitant use of inhaled steroids. The use of  $\beta$ -2 agonists as monotherapy was still reported in 25% of athletes applying for their use in the 2010 Olympics [9].

In conclusion, our data indicate that intense and chronic exercise is associated, in Olympic athletes, with a higher prevalence of asthma, airway

hyperresponsiveness, allergic sensitizations and infections, as well as with immune changes suggestive of a Th2 phenotype. These findings should call for adequate medical, environmental and logistic policies on the occasion of the future Olympic Games. They might also provide useful practical hints for better management of the many competitive and noncompetitive exercisers with asthma and allergy.

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## Conflicts of interest

*All authors significantly contributed to the study conception and design, data acquisition, analysis and interpretation, drafting of the article or revising it critically and final approval of the version to be submitted. No author has conflicts of interest to disclose.*

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